EMULSION PRECONCENTRATE COMPRISING A CYCLOSPORIN AND ACETYLATED MONOGLYCERIDE

TECHNICAL FIELD

The invention is directed to pharmaceutical compositions which facilitate the administration of cyclosporins.

BACKGROUND ART

The term "solvent system" as used herein refers to a carrier in which an active drug (i.e. a cyclosporin) is dissolved. The solvent system may be a single solvent or a mixture of ingredients included as solvents, surfactants, diluents, or for other purposes.

The term "cyclosporin" as used herein refers to any member of a class of nonpolar polypeptides, as defined in the Merck Index, Twelfth Edition. One such cyclosporin is cyclosporin A, also known as "cyclosporine" and hereinafter referred to as "cyclosporine", known to be therapeutically active as an immunosuppressant.

Cyclosporins are hydrophobic and have low solubility in aqueous media. This makes it difficult to design pharmaceutical compositions (i.e. dosage forms) comprising cyclosporins which exhibit satisfactory absorption into systemic circulation after oral administration, or absorption into the target tissue upon topical administration.

The cyclosporin can be dissolved in an organic solvent (e.g. ethanol or propylene glycol), but if the solvent is water-miscible, when the composition is mixed with gastrointestinal fluid or other aqueous medium, the cyclosporin will precipitate.

Methods of overcoming this problem are now known in the prior art. The most common approach is to dissolve the cyclosporin in a solvent system that comprises at least one lipophilic (hydrophobic) solvent and a surfactant, so that the composition disperses into an emulsion when mixed into gastrointestinal fluid or other aqueous medium.

Such compositions are called "emulsion preconcentrates".

U.S. patent 4388307 discloses such compositions. A commercial product that has been sold under the trademark "Sandimmune" is made according to U.S. patent 4388307, and, more specifically, comprises cyclosporine dissolved in a solvent system comprising ethanol as hydrophilic solvent, a vegetable oil as lipophilic solvent, and a surfactant. The ethanol is required to dissolve the cyclosporin in the composition as the vegetable oil has inadequate capacity to dissolve cyclosporins. While this composition is superior to previously known compositions, it still exhibits absorption that is less than the maximum possible and is variable. Moreover, the use of ethanol has disadvantages, as ethanol is volatile, and Sandimmune capsules must be individually packaged in metallic pouches to avoid evaporation of the ethanol.

U.S. patent 5342625 discloses compositions that are superior in certain respects to the compositions taught in the prior reference. The compositions of U.S. patent 5342625 also comprise, in addition to the cyclosporin, a hydrophilic solvent, a lipophilic (i.e. hydrophobic) solvent and a surfactant. Again, the hydrophilic solvent is an alcohol and more particularly a polyol which consists of either propylene glycol or a pharmaceutically acceptable alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol. This reference teaches that only lipophilic solvent that is not miscible with the selected hydrophilic solvent is suitable for the purpose of this invention.

It is also disclosed that compositions according to U.S. patent 5342625, when added to water, disperse into emulsions with droplet size of less than 2000Å, which is smaller than obtained with prior art compositions, thus leading to improved absorption.

Emulsions with droplet size of less than 2000Å are defined as "microemulsions". Compositions that, upon addition to water, disperse into microemulsions are called "microemulsion preconcentrates".

UK Patent Application No. 2 270 842 published March 30, 1994 relates to pharmaceutical compositions comprising cyclosporin in a carrier medium; the carrier comprises:

(i) a hydrophilic organic solvent in the form of a polyol and/or a lower alkanol such as propylene glycol and ethanol;

(ii) a lipophilic solvent; and

(iii) a polyoxyethylene-sorbitan-fatty acid ester surfactant.

Canadian Patent 2072509 discloses microemulsion preconcentrates comprising a cyclosporin dissolved in a carrier which comprises:

(i) as hydrophilic solvent, propylene glycol, either alone or with other lower alkanols e.g. ethanol;

(ii) as lipophilic solvent a mixed mono-, di- and tri-glyceride; and

(iii) a surfactant.

Again the hydrophilic solvent and the lipophilic solvent are not intermiscible.

The compositions of Canadian Patent 2072509 appear to be within the scope of Claim 1 of US Patent 5342625, but limited to propylene glycol as hydrophilic solvent and a mixed mono-, di-, and tri-glyceride as lipophilic solvent.

A composition made according to the disclosure of Canadian patent 2072509 is now marketed under the trademark "Neoral", in the form of both an oral liquid which is a microemulsion preconcentrate intended to be diluted into an aqueous drink before ingestion, and a soft gelatin capsule containing the microemulsion preconcentrate.

For both the soft gelatin capsules and the oral liquid, the labelling indicates that the "Neoral" emulsion preconcentrate comprises cyclosporine dissolved in ethanol and propylene glycol as hydrophilic solvents, corn oil glycerides as lipophilic (hydrophobic) solvent, and polyoxyl 40 hydrogenated castor oil as surfactant. It also contains dl-alpha-tocopherol at a level of about one percent by weight as antioxidant. Although Canadian patent 2072509 includes some examples without ethanol, the use of ethanol in the commercial "Neoral" product indicates that compositions without ethanol either were not found to give adequate stability or were not found to give adequate absorption upon ingestion.

While Neoral does enable improved absorption relative to Sandimmune, it still has certain undesirable properties. Specifically:

1. Ethanol is volatile, so that the soft gelatin capsules have to be packaged individually in metallic pouches to prevent evaporation of the ethanol.

2. Ethanol contributes to an undesirable taste of the microemulsion preconcentrate, so that, even after dilution into a sweetened drink, there is still a somewhat unpleasant taste.

3. The lipophilic solvent, which is mixed mono- di- and tri-glycerides, is relatively expensive.

Several prior art publications disclose further improvements achieved by selecting different lipophilic and/or hydrophilic solvents.

International Publication Number W094/25068 discloses improved compositions in the form of microemulsion preconcentrates in which the principal solvent for the cyclosporin is an alcohol which is selected from alcohols having a boiling point above 100°C and a solubility in water of under 10 g per 100 g at 20°C. Because such alcohols are good solvents for cyclosporine, they eliminate the need for ethanol. Preferred alcohols, within the scope of the disclosure of W094/25068, are saturated alkyl alcohols having 8 to 14 carbon atoms per molecule, including 1-octyl, 2-octyl, 1-decyl, 1-dodecyl and 1-tetradecyl alcohols. However, a problem with such compositions is that the selected alcohols are more toxic than other lipophilic solvents generally used in the art.

New Zealand Patent Application No. 280689 discloses improved microemulsion preconcentrates in which a cyclosporin is dissolved in a solvent system comprising a lipophilic (hydrophobic solvent), a hydrophilic solvent and a surfactant, wherein the lipophilic solvent is selected from tocol, tocopherols and tocotrienols, and derivatives thereof, including specifically Vitamin E. The lipophilic solvent and hydrophilic solvent again are not intermiscible. While these compositions exhibit improved properties over the prior art, such lipophilic solvents are relatively expensive.

In light of the difficulties with prior art compositions, it is an object of the within invention to enable compositions with the advantages of those disclosed in US Patent 5342625 and Canadian Patent 2072509, which comprise a lipophilic solvent that is inexpensive and that is also a relatively good solvent for cyclosporins, so as reduce the cost of the composition and also reduce or eliminate the need for ethanol in the composition.

SUMMARY OF THE INVENTION

It has been unexpectedly found that such advantages can be achieved and the drawbacks of the prior art surmounted when using as lipophilic solvent acetylated monoglycerides. Acetylated monoglycerides are inexpensive and exhibit ideal properties for use as lipophilic (hydrophobic) solvent in cyclosporin emulsion preconcentrates.

The present invention thus provides a pharmaceutical composition in the form of an emulsion preconcentrate comprising a cyclosporin dissolved in a solvent system comprising acetylated monoglycerides, and a surfactant.

In a further embodiment such pharmaceutical composition is in the form of a microemulsion preconcentrate.

DETAILED DESCRIPTION OF THE INVENTION

As aforesaid, an essential component of an emulsion preconcentrate is a lipophilic solvent, and it has been found that acetylated monoglycerides function surprisingly well as lipophilic solvent in cyclosporin emulsion preconcentrates.

It will be understood that acetylated monoglycerides consist of glycerol esterified with fatty acids at one of the three hydroxyl functions, with the other two hydroxyls replaced by an acetyl moeities.

Acetylated monoglycerides are sold in the United States under the tradename "Myvacet" by Eastman Chemical Products Inc. They are made by reacting fats with glycerol and triacetin.

By adjusting the degree of saturation of the monoglyceride and the degree of acetylation, different characteristics are obtained.

Fully acetylated monoglycerides prepared from unsaturated monoglycerides are liquids at room temperature. In this context, the phrase "fully acetylated" is intended to mean having a minimum acetylation of about 96%.

Fully acetylated monoglycerides are currently available from Eastman Chemical Product Inc. under the designations Myvacet 9-08 and Myvacet 9-45. For Myvacet 9-08, the fat source is hydrogenated coconut oil. For Myvacet 9-45 the fat source is partially hydrogenated soybean oil.

Myvacet 9-08 and Myvacet 9-45 are both liquids at room temperature, having melting points of 4°C to 12°C. Both are well suited for use as lipophilic solvent, but Myvacet 9-45 is especially preferred because of its lower cost.

In comparison to other ingredients used in the prior art as lipophilic solvent, these acetylated monoglycerides offer the following advantage:

1. Low cost.

2. They are good solvents for cyclosporins, thus reducing the amount of lipophilic solvent required and/or reducing the need for a hydrophilic co-solvent to maintain the cyclosporin in a stable solution.

3. They are readily inter-dissolved with preferred hydrophilic co-solvents. For example, they are entirely miscible with propylene carbonate.

4. They become readily dispersible into emulsions or microemulsions upon inclusion of a suitable surfactant.

Because of the aforesaid properties, acceptable emulsion preconcentrates or microemulsion preconcentrates can be made using only the active drug (i.e. a cyclosporin), acetylated monoglycerides, and a surfactant.

However, preferred compositions will also comprise a hydrophilic solvent (i.e. a solvent having solubility of at least 1 g per 100 g in water at 20°C) as co-solvent. This is because suitable hydrophilic solvents are more efficient than acetylated monoglycerides as solvents for cyclosporin. Inclusion of a suitable hydrophilic solvent can thus reduce the total amount of solvent needed, thereby increasing the achievable concentration of the cyclosporin in the composition.

Suitable hydrophilic solvents will include, for example, ethanol, propylene glycol, propylene carbonate, benzyl alcohol, and polyethylene glycol having mean molecular weight of less than about 1000.

It is preferable to avoid use of ethanol because of its volatility. The preferred hydrophilic solvents are propylene glycol and propylene carbonate. Propylene carbonate is most preferred because of its complete miscibility with acetylated monoglycerides.

The fact that a microemulsion preconcentrate can be made using acetylated monoglyceride as lipophilic solvent and propylene carbonate as hydrophilic solvent, despite the fact that they are miscible with each other, is contrary to the teaching of U.S. patent 5342625.

The compositions of the present invention will also include at least one surfactant, by which is meant a compound with both lipophilic and hydrophilic properties, which improves the dispersibility of the composition into an emulsion or microemulsion in water.

Suitable surfactants include those cited in U.S. patent 5342625 and Canadian patent 2072509.

Preferred surfactants are polyoxyethylene glycolated natural or hydrogenated vegetable oils; for example, polyoxyethylene glycolated natural or hydrogenated castor oil. Particularly preferred is the surfactant designated in the United States Pharmacopoeia and National Formulary as Polyoxyl 40 Hydrogenated Castor Oil, which is available under the tradename "Cremophor RH40".

It has been surprisingly found that these preferred surfactants act synergistically with other surfactants, so that inclusion of a second surfactant as co-surfactant can reduce the total amount of surfactant needed, without loss of effectiveness in enabling dispersion into an emulsion or microemulsion.

Preferred surfactants for use as co-surfactant are polyoxyethylene-sorbitan-fatty acid esters; e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g. products of the type known as polysorbates and available under the tradename "Tween". Especially preferred as co-surfactant is polyoxyethylene 20 sorbitan monolaurate, which is also known as polysorbate 20.

Compositions in accordance with the invention may also contain other ingredients.

For example, the composition may include, in addition to the foregoing, one or more other ingredients that are included as diluents, thickening agents, anti-oxidants, flavouring agents, and so forth.

Compositions in accordance with the invention may be liquids at ambient temperature or they may be solids prepared, for example, by use of one or more ingredients with melting point above ambient temperature. The ingredients may be blended at a temperature above the melting point and then used to fill capsules while still molten, or cooled to form solids. The solids may be ground into granules or powder for further processing; for example, filling capsules or manufacture of tablets.

If it is desired to increase the melting point to ensure that the composition is a solid at room temperature, this may be accomplished by adding a further ingredient with a relatively high melting point, such as, for example, polyethylene glycol with average molecular weight of above 1000.

Capsules or tablets may be further process by applying coatings thereto.

Compositions in accordance with the invention may comprise dosage forms for direct administration as emulsion preconcentrates or microemulsion preconcentrates. For example, an emulsion preconcentrate or microemulsion preconcentrate may be directly used as liquid for oral ingestion, parenteral use, or topical application or it may be encapsulated into gelatin capsules for oral ingestion.

However, the present invention also provides pharmaceutical compositions in which the emulsion preconcentrate or microemulsion preconcentrate is further processed into an emulsion or a microemulsion. Thus where oral administration is practised, emulsions or microemulsions obtained, e.g. by diluting a preconcentrate with water or other aqueous medium (for example, a sweetened or flavoured preparation for drinking), may be employed as formulations for drinking. Similarly, where topical application is intended, compositions comprising an emulsion preconcentrate, a thickening agent, and water will provide an aqueous emulsion in gel, paste, cream or like form.

Compositions in accordance with the present invention, whether emulsion preconcentrates, microemulsion preconcentrates, emulsions, or microemulsions, may be employed for administration in any appropriate manner and form; e.g. orally, parenterally, topically; or rectally.

The relative proportion of the cyclosporin and other ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned; e.g. whether it is an emulsion preconcentrate, microemulsion preconcentrate, emulsion, or microemulsion, the route of administration, and so forth. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the composition; e.g. in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of persons skilled in the art.

The invention will be more fully understood by the following examples which are illustrative but not limiting of compositions in accordance with the present invention.

EXAMPLES

In the following example, the ingredients were weighed into a test tube in the proportions shown, the test tubes and contents were warmed to 100°C in a water bath, and then the test tubes were shaken until the contents of each tube were interdissolved to form a clear solution.

Example A:

Cyclosporine	1.0
Myvacet 9-45	6.0
Cremophor RH40	3.7
	10.7

Then 1 g of the resulting emulsion preconcentrate was transferred to another test tube, about 20 mL of water was added, and the test tube was shaken. The preconcentrate dispersed to form an emulsion.

In each of the following examples, the ingredients were weighed into a test tube in the proportions shown, the test tubes and contents were warmed to 100°C in a water bath, and then the test tubes were shaken until the contents of each tube were interdissolved to form a clear solution.

Then 1 g from the resulting emulsion preconcentrate in each test tube was transferred to another test tube, about 20 mL of warm (37°C) water was added, and the test tube was shaken to disperse the 1 g of the composition in the water to form an emulsion or microemulsion. The resultant emulsions or microemulsions were then compared for clarity by measuring the light transmittance through a 1 cm cell at 600 nm. A higher transmittance indicates a smaller droplet size and hence, a finer emulsion or microemulsion.

Example No.	1	2	3	4
Cyclosporine	1.0	1.0	1.0	1.0
Myvacet 9-45	2.7	2.5	2.3	2.1
Propylene Glycol	1.6	1.6	1.6	1.6
Cremophor RH40	3.6	3.6	3.6	3.6
Polysorbate 20	1.8	2.0	2.2	2.4
Total:	10.7	10.7	10.7	10.7
Percent Transmittance at 600 nm	87.3	89.3	91.4	91.4

Example No.	5	6	7	8
Cyclosporine	1.0	1.0	1.0	1.0
Myvacet 9-45	2.7	2.5	2.3	2.1
Propylene Carbonate	1.6	1.6	1.6	1.6
Cremophor RH40	3.6	3.6	3.6	3.6
Polysorbate 20	1.8	2.0	2.2	2.4
Total:	10.7	10.7	10.7	10.7
Percent Transmittance at 600 nm	87.5	89.4	91.6	91.4

As aforesaid, the transmittance is that of an emulsion or microemulsion made by dispersing 1 g of the composition in about 20 mL of warm (37°C) water.

In each case, the density of the preconcentrate was about 1.07 g/mL, so that each mL of the preconcentrate contained about 100 mg of cyclosporine.

As a basis for comparison, 1 g of the marketed product, Neoral Oral Solution, was similarly dispersed in about 20 mL of warm (37°C) water and the transmittance through 1 cm cell at 600 nm was measured to be 83.9%. The compositions of all of examples 1 to 8 thus all gave higher transmittance than Neoral, which indicates that the microemulsions are at least as fine as obtained with Neoral.